

Tumor Spread and Outcome of Treatment in Primary Esophageal Small Cell Carcinoma

TADASHI NISHIMAKI, MD,* TSUTOMU SUZUKI, MD, SATORU NAKAGAWA, MD,
KAZUO WATANABE, MD, KIKUO AIZAWA, MD, AND KATSUYOSHI HATAKEYAMA, MD
The First Department of Surgery, Niigata University School of Medicine, Niigata, Japan

Background: The most effective treatment for patients with esophageal small cell carcinoma has not yet been established because of the overall extremely poor prognosis regardless of the mode of treatment. The role of esophagectomy has been controversial in the management of patients with this disease.

Methods: The clinicopathologic characteristics of 13 patients with primary esophageal small cell carcinoma were retrospectively studied and the prognostic significance of various factors with respect to esophagectomy were evaluated.

Results: Lymph node metastases and distant metastases were found at the time of presentation in 92.3 and 46.2%, respectively. Two of nine patients treated by surgical resection for local-regional disease survived >5 years after radical esophagectomy with a projected 5-year survival rate of 22.2%. The remaining 4/13 patients were treated by nonsurgical modalities, but died of the disease within 10 months. A significant difference ($P < 0.05$) was detected between the survival curves of the two groups of patients.

Conclusion: Radical esophagectomy may be an effective treatment modality in improving survival and the odds of a cure in patients with local-regional small cell carcinoma of the esophagus. *J. Surg. Oncol.* 64:130–134. © 1997 Wiley-Liss, Inc.

KEY WORDS: esophageal neoplasms; pathology; surgery; esophagectomy; surgical oncology; esophagus

INTRODUCTION

Although small cell carcinoma (SCC) usually originates in the lung, SCC has been reported rarely to develop in the esophagus since the first description by McKeown in 1952 [1]. The incidence of this rare esophageal tumor has been estimated to range from 0.8% to 2.4% of all esophageal malignancies [2]. As is true in pulmonary SCC, the prognosis of patients with esophageal SCC has been extremely poor regardless of the mode of treatment, including surgical resection, chemotherapy, and radiotherapy. So far, cured cases have not been reported in patients with esophageal SCC. Because of the rarity of this disease and a paucity of successfully

treated cases, the most effective treatment to improve long-term survival and effect a cure in patients with esophageal SCC has been unresolved.

The objectives of the present study were to clarify the characteristics of tumor spread in esophageal SCC and to find an effective treatment modality to achieve cure in patients with the disease by reviewing our own series.

*Correspondence to: The First Department of Surgery, Niigata University School of Medicine, Asahimachi-dori 1-757, Niigata 951, Japan.

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MATERIALS AND METHODS

Patients

During the period 1974–1994, 809 patients with esophageal carcinoma were treated in the First Department of Surgery (Niigata University). Of those patients, 13 (1.6%) had a primary esophageal tumor histologically indistinguishable from pulmonary SCC and were included in the present study. Of the 13 patients with esophageal SCC, nine underwent a subtotal esophagectomy and the remaining four were treated without esophageal resection. The age of the patients ranged from 50–78 years (average, 63.5 years). All but one patient were men.

Preoperative Staging

Preoperative diagnostic and staging procedures generally included a physical examination, routine laboratory examinations, a chest radiograph, upper gastrointestinal barium studies, endoscopy and biopsy, endoscopic ultrasonography, computed tomography (CT) of the chest and abdomen, and ultrasonography of the neck and abdomen. The chest radiograph, fiberoptic bronchoscopy, or pathologic findings at surgery were used to eliminate the lung as a possible primary site.

Esophagectomy

If esophageal resection was performed, esophagectomy was considered curative when the tumor was removed completely en bloc and was considered palliative when the clearance of tumor was either grossly or microscopically incomplete. Esophageal resection was termed a radical esophagectomy when performed along with systematic mediastinal and abdominal lymphadenectomies with the intent to cure.

Diagnostic Criteria

All of the esophageal tumors found in the 13 patients were histologically diagnosed as SCC either on the biopsy specimens or esophagectomy specimens based on the World Health Organization (WHO) histological typing of lung tumors [3] and were subclassified into oat cell carcinoma and intermediate cell type, using this diagnostic criteria.

Evaluation of Tumor Spread

The extent of tumor spread was clinically or histologically evaluated using the TNM classification of the American Joint Committee on Cancer [4]. In those who underwent esophageal resection initially, staging was based on intraoperative findings and pathologic assessment. In those who were treated by nonsurgical modalities or received preoperative chemotherapy, tumor spread was evaluated using imaging techniques before the initiation of treatment.

Follow-up

Follow-up data were available for all cases. Patients were followed regularly at our institution or affiliated hospitals with routine physical and laboratory examinations after discharge. Chest radiographs, ultrasonography, or CT scans were performed annually to detect possible recurrent disease.

Statistical Analysis

Survival time was calculated from the date of initiation of the treatment until the date of death or most recent follow-up. Cumulative survival rates after the treatment were examined using the Kaplan-Meier method. The equality of the survival curves was assessed using the generalized Wilcoxon test. Differences between means were assessed by Student's *t*-test. A *P* value of <0.05 was regarded as indicating a significant difference.

RESULTS

Tumor Spread

The primary sites and the depth of tumor invasion of esophageal SCC in the 13 patients are summarized in Table I. The mean size of the tumors was 7.4 cm. A significant difference in size ($P < 0.05$) was detected between the nine tumors surgically resected [mean \pm standard deviation (SD): 5.5 ± 3.9 cm] and the four tumors treated by nonsurgical modalities (mean \pm SD: 11.7 ± 2.1 cm). Lymph node metastases were found in 12 (92.3%) of the 13 patients either at clinical staging or intraoperatively. Furthermore, distant metastases were present in six patients (46.2%) at the time of initiation of treatment: two patients had liver metastases and five patients had metastases to distant lymph nodes, including the cervical, abdominal, and axillary lymph nodes. All of the eight patients undergoing esophagectomy without preoperative treatment had positive vessel invasion (Table I).

Outcome of Treatment

Treatment modalities performed with the subsequent outcome in the 13 patients are summarized in Table II. The nine patients who were evaluated as having no distant metastases at preoperative staging were treated by esophagectomy, either alone or in combination with chemotherapy or radiotherapy. In the other four patients, tumor invasion to the adjacent vital organs was evident with or without distant metastases at staging, and they were therefore, nonsurgically treated. The overall median survival was 10 months for all patients; the 1- and 5-year survival rates were 30.8% and 15.4%, respectively.

In the nine patients surgically treated, esophagectomy was performed initially with the intent to cure. However, liver metastasis and extensive cervical lymph node metastases were found at surgery in two patients. As a re-

TABLE I. Tumor Spread in Esophageal Small Cell Carcinoma

Case No.	Primary site ^a	Depth of tumor invasion ^b	Length of tumor (cm)	Lymph node metastasis	Vessel invasion	Distant metastasis ^c	TNM Stage
1	L	p-T 1(sm)	8.4	+	+	—	II B
2	M	p-T 1(sm)	3.0	+	+	LN	IV
3	M	p-T 1(sm)	2.3	+	+	—	II B
4	M	c-T 3	11.0	—	NA	—	II A
5	M	p-T 2	2.4	+	+	Liver	IV
6	L	p-T 3	7.6	+	+	—	III
7	L	p-T 3	12.5	+	+	—	III
8	M	p-T 3	9.7	+	+	LN	IV
9	M	p-T 3	3.7	+	+	—	III
10	M	c-T 4	14.0	+	NA	LN, liver	IV
11	M	c-T 4	11.6	+	NA	LN	IV
12	M	c-T 4	12.0	+	NA	LN	IV
13	M	c-T 4	9.0	+	NA	—	III

^aL: lower esophagus; M: middle esophagus.

^bp-: pathologically assessed; c-: clinically assessed.

^cLN: lymph node.

NA: not assessed.

sult, palliative esophagectomy was performed in the two patients. In one of the other seven patients who underwent a radical esophagectomy, the operation was postoperatively regarded as palliative because a positive proximal margin was found on histologic examination of the resected specimen. Therefore, a curative esophagectomy was performed in six of the nine patients. No patients died within 30 days of the operation. Esophagectomy was the single treatment modality in four of the nine patients because of associated medical disease or poor performance status after operation. Five of the nine patients were further treated by chemotherapy or radiotherapy in addition to radical esophagectomy. Of these patients, two are surviving >5 years after esophageal resection without any evidence of tumor recurrence. One patient (Case No.4) received preoperative chemotherapy using cisplatin for a T3 oat cell carcinoma, resulting in complete disappearance of the gross tumor. However, a residual microscopic lesion of combined squamous cell carcinoma was found in the resected specimen. This patient has survived 106 months after esophagectomy and additional postoperative chemotherapy. Another patient (Case No.7) was found to have a T3 intermediate cell type SCC with metastases to three of the mediastinal lymph nodes and two of the perigastric lymph nodes after radical esophagectomy. This patient has survived 64 months after four cycles of postoperative combination chemotherapy of cisplatin and 5-fluorouracil. Median survival for the nine patients treated surgically was 11 months; the projected 5-year survival rate was 22.2% (Fig. 1).

Of the four patients treated by nonsurgical modalities, one received chemotherapy consisting of cisplatin and 5-fluorouracil for a T4 oat cell carcinoma with multiple liver metastases. The patient died of the disease 2 months

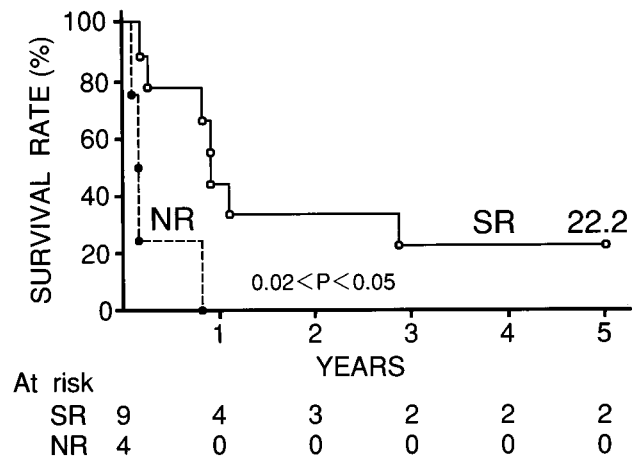


Fig. 1. Cumulative survival curves for patients with esophageal small cell carcinoma treated by surgical resection (SR) and for patients treated with no surgical resection (NR). A significant difference was detected ($P < 0.05$) between the two survival curves.

after the chemotherapy showing a temporary disappearance of the liver metastases. Another patient was treated by multimodality treatment consisting of chemo-, radio-, and hyperthermotherapy but died of liver metastases 10 months after the treatment began. The patient had almost complete disappearance of the primary tumor and lymph node metastases, as documented by esophagogram and CT scan. The remaining two patients received no active antitumor treatment because of their poor performance status. Median survival for the four patients treated by nonsurgical modalities was 2 months, and none of these patients survived >1 year. There was a significant difference in survival between the patients undergoing an esophagectomy and those treated by nonsurgical modalities ($P < 0.05$) (Fig. 1).

Recurrent disease occurred in 9 of 11 patients who

TABLE II. Treatment Modalities and Outcomes for Esophageal Small Cell Carcinoma

Case no.	Modalities ^a	Type of resection	Chemotherapy regimen	Radiation dose	Relapse	Survival period (mo)	Vital status ^b
1	S/C, R	Palliative	BLM 7.5 mg, IM \times 10 times	55Gy	Bone	11	DOD
2	S	Curative	—	—	Local, pleura	11	DOD
3	S/C	Curative	CDDP 80 mg/m ² , IV, d1 VP-16 70 mg/m ² , IV, d1-4] \times 2 course	—	Cervical LN, Lung	10	DOD
4	C/S/C	Curative	CDDP25 mg, IV \times 5 times (preoperatively) CDDP 75 mg, IV \times 2 times (postoperatively)	—	—	106	NED
5	S/C	Palliative	CDDP 70 mg/m ² , IV Vindesine 3 mg/m ² , IV] \times 3 course	—	Local, liver Cervical LN	13	DOD
6	S	Curative	—	—	Liver	3	DOD
7	S/C	Curative	CDDP50 mg/m ² , IV, d1 5FU 300 mg/ml ² , IV, d1-5] \times 4 course	—	—	64	NED
8	S	Palliative	—	—	Local, lung Abdominal LN	34	DOD
9	S	Curative	—	—	Bone, liver, skin	2	DOD
10	C	—	CDDP 80 mg/m ² , IV, d1 5FU 800 mg/m ² , IV, d1-5] \times 2 course	—	Bone, liver, pancreas	2	DOD
11	NAT	—	—	—	—	1	DOD
12	C,R,HT	—	CDDP 25 mg, IV \times 8 times	60Gy	Liver	10	DOD
13	NAT	—	—	—	—	2	DOD

^aS: surgical resection; C: chemotherapy; R: radiotherapy; NAT: no active treatment; HT: hyperthermotherapy; /: prior to.

^bDOD: died of disease; NED: alive with no evidence of recurrent disease.

received active antitumor treatment. Although local recurrence developed in three patients, all of the nine patients had distant organ metastases (Table II).

DISCUSSION

Aggressive biological behavior as characterized by early dissemination and a rapidly fatal course is a well-known property of esophageal SCC. The present study has confirmed the high metastatic potential of this tumor even at an early stage of local extension. Vascular invasion in the esophageal wall was found in 100% and lymph node metastases in 92.3% of cases in our series. Furthermore, distant metastases had already developed in 46.2% of our patients before starting treatment. These results are consistent with those reported by Isolauri et al. [5] in which 62.5% of patients with esophageal SCC had distant metastases at the time of diagnosis.

Effective treatment to improve long-term survival and increase the cure rate in patients with esophageal SCC has not yet been established, because of the rarity of this disease and a paucity of successfully treated cases regardless of treatment modalities used. McFadden et al. [6] analyzed survival data obtained from 85 cases of esophageal SCC in the world literature and estimated the mean overall survival to be only 5.1 months from the time of diagnosis. The first case of esophageal SCC in which a partial response was achieved by chemotherapy alone was reported by Kelsen et al. in 1980 [7]. Since then, chemotherapy, particularly multidrug combination chemotherapy, has been used as the first line of manage-

ment with or without radiotherapy because of the high incidence of distant metastases at the time of presentation and a relatively high sensitivity of SCC to chemoradiotherapy [8,9]. Although partial or complete remission has been reported in some patients with esophageal SCC, chemotherapy alone has not yet succeeded in prolonging the survival of the patients. Furthermore, Nichols and Kelsen [9] have reported that 50% of patients with esophageal SCC did not respond to chemotherapy and 33% of patients did not respond to radiotherapy. Recently, McCullen et al. [10] have reported a case of esophageal SCC with distant metastases surviving 3 years after supralethal chemoradiotherapy with autologous bone marrow transplantation. However, this patient ultimately died of extensive recurrent disease, indicating that total eradication of tumor cells is unlikely even with supralethal aggressive chemotherapy. The longest survival reported so far has been 72 months, which was achieved by curative esophagectomy with adjuvant chemotherapy and subsequent radiotherapy to the paraaortic recurrence in the abdomen [11].

Curative resection achieved by radical en bloc esophagectomy may offer the best chance for long-term survival in patients with esophageal SCC as long as the disease remains local or regional. Lieberman et al. [12] found that the longest median survival time (28 months) was obtained in patients treated by esophagectomy in combination with chemotherapy in their review of 107 previously reported cases of esophageal SCC. One patient in the series reported by Law et al. [11] survived >5

years after curative esophagectomy. Moreover, two patients with local-regional disease in our series have survived >5 years after radical esophagectomy with systemic chemotherapy. In contrast with the cases treated by esophagectomy, so far 5-year survival has not yet been reported in patients with esophageal SCC treated by non-surgical treatment modalities. Although the rarity of this disease precludes controlled trials of esophagectomy for prolonging the survival period of the patients, we believe that radical esophagectomy offers patients an increased possibility of survival. Furthermore, our opinion may be supported by the facts that not all SCCs are chemo- or radiosensitive, that esophageal SCCs are frequently associated with other histologic types of carcinoma, which may be less sensitive to chemoradiotherapy [13], and that operative mortality rates are now acceptably low even in cases of radical en bloc esophagectomy (<5%) [14,15]. Theoretically, surgical resection may lessen the risk of emergence of drug-resistant tumor cell clones during prolonged chemotherapy. In addition, the role of surgical resection as an effective treatment modality for pulmonary SCC has been re-evaluated and a significant percentage of curative resections were achieved in the most recent studies particularly in patients with limited disease [16].

In conclusion, esophageal SCC is an aggressive tumor with a high metastatic potential, which carries a very poor prognosis. Systemic chemotherapy is needed to control the probable distant metastases. However, we consider radical esophagectomy to be the most essential treatment modality to improve survival and cure rates in patients with local-regional SCC of the esophagus.

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